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REMARKS

Clarification of the Restriction Requirement and Disposition of Claims

In the Office Action dated March 21, 2003 (Paper No. 13), the claims were restricted under 35 U.S.C. § 121 into the following groups:

I. Claims 1-56, and 63, drawn to a conjugate of wild-type FVII or FVIIa, classified in class 530, subclass 350. It is noted that claim 63 is drawn to a composition comprising a conjugate. New claims 68-92 and 103-105 presented June 19, 2003 are drawn to a conjugate and a composition comprising a conjugate, respectively.

II. Claim 57, drawn to a polypeptide, classified in class 536, subclass 350. New claims 93-95 presented June 19, 2003 are drawn to a polypeptide.

III. Claims 58-61, drawn to a nucleotide, expression vector, and host cell, classified in class 536, subclass 23.1, class 435, subclass 320.1, and class 435, subclass 325. New claims 96-102 presented June 19, 2003 are drawn to nucleotides, expression vectors, and host cells.

IV. Claim 62, drawn to a method for producing a conjugate, classified in class 530, subclass 350. New claims 113-116 presented June 19, 2003 are drawn to a method for producing a conjugate.

V. Claims 64-67, drawn to a method of treatment, classified in class 530, subclass 350. New claims 106-110 presented June 19, 2003 are drawn to a method of treatment.

In the Preliminary Amendment/Response to restriction dated June 19, 2003 (Paper No. 15A), Applicants provisionally elected Group I, drawn to a conjugate and a composition comprising the conjugate, with traverse. Applicants submitted that co-examination of Group I and Group II (drawn to a polypeptide) would not present a serious burden to the Examiner. In the Office Action dated August 12, 2003 (Paper No. 16), the Examiner noted that Groups I and II were rejoined.

Furthermore, in the Office Action dated March 21, 2003 (Paper No. 13), the Group I claims were restricted to a single patentably distinct species for examination in this application. In the Preliminary Amendment/Response to Restriction dated June 19, 2003 (Paper No. 15A),

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Applicants provisionally elected the species SEQ ID NO:1 comprising the substitution T106N, with traverse, and had requested the Examiner reconsider his position in view of the arguments presented, and to consider a species election rather than a restriction. The Examiner made the restriction final in Paper No. 16. The Examiner's reasoning was the following: "Applicant's traversal points out that MPEP 803.04 entitles the applicant to elect ten nucleotide sequences. The examiner does not find this argument persuasive, as it is amino acid sequences that are being searched. The requirement is still deemed proper and is therefore made final".

For the record, it is respectfully submitted that the Examiner may have inadvertently overlooked the following passage in Applicants' request for reconsideration in paper No. 15A:

As noted in MPEP 803.04, 3rd paragraph, "[it] has been determined that normally ten sequences constitute a reasonable number for examination purposes" and, in the 4th paragraph of that section, "[in] some exceptional cases, the complex nature of the claimed material, for example a protein amino acid sequence reciting three dimensional folds, may necessitate that the reasonable number of sequences to be selected be less than ten." (*emphasis added*)

Applicants are under the impression from the above that MPEP 803.04 is not solely limited to nucleotide sequences.

Solely to expedite prosecution, Applicants are amending independent claim 68 herein to recite only the elected substitution, and canceling claims 71-74, 78-80, and 84, without prejudice to renewal or filing in one or more divisional or continuation applications, as drawn to non-elected substitutions. These amendments and claim cancellations are not to be construed as agreement with the Examiner's position or abandonment of any previously claimed subject matter. Applicants reserve the right to petition pursuant to 37 CFR 1.144 and MPEP 818.03(c).

In the Preliminary Amendment /Response to Restriction dated June 19, 2003 (Paper No. 15A), Applicants had noted that pending claims 68-70, 75-77, 81-83, and 85-116 all read on the elected invention SEQ ID NO:1 comprising the substitution T106N. However, in the Office Action dated August 12, 2003 (Paper No. 16), it was stated that "claims 68-70, 85-89, 91-95, and 103-105 are pending and will be examined to the extent they read on SEQ ID NO:1". In the Office Action Summary, under "Disposition of Claims", Box 4 indicates that Claim(s) 68-70, 85-

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89, 91-95, and 103-105 are pending in the application. There is no indication of the status of the remaining claims introduced in Applicants' Preliminary Amendment dated June 19, 2003 (Paper No. 15A), in which claims 68-116 were presented. It is to be noted that none of claims 68-116 have been canceled by Applicants prior to the present amendment.

When a restriction requirement is traversed, the Examiner cannot cancel claims to the non-elected invention without authorization from Applicants. MPEP §821.01 sets forth the appropriate treatment of claims to a non-elected invention when the election was made with traverse (e.g., Form Paragraph 8.05), which serves to acknowledge that Applicants have retained the right to petition the requirement under 37 CFR §1.144. No such acknowledgement of the status of claims to the non-elected invention was made in Paper No. 16, contrary to Patent Office procedure as set forth in MPEP §821.01.

In addition, it appears several claims directed to the elected invention have not been accounted for in Paper No. 16. It is to be noted that previously-presented claims 75-77 and 81-83 (which are not listed anywhere in the Office Action Summary "Disposition of Claims" of Paper No. 16) incorporated all the limitations of the elected invention. These claims originally depended from claim 69 as originally presented. Claim 69, by way of the present amendment, now also incorporates all the limitations of claim 85. According to Box 4 of the "Disposition of Claims" of Paper No. 16, both claims 69 and 85 were pending in the present application, so one would conclude that claims 75-77 and 81-83 should also be pending in this application. Likewise, claim 90 (which also does not appear in the Office Action Summary), depends from claim 89 which is listed in Box 4 of the "Disposition of Claims". Applicants wish to clarify that claim 90 as previously presented had erroneously depended from claim 82 rather than claim 89 as intended; that error in dependency is corrected here. For these reasons, Applicants believe that the exclusion of claims 75-77, 81-83, and 90 was inadvertent, and will operate on the assumption that these claims are also pending in the present application.

Furthermore, according to 37 CFR §1.142:

(b) Claims to the invention or inventions not elected, if not canceled, are nevertheless withdrawn from further consideration by the examiner by the election, subject however to reinstatement in the event the requirement for restriction is withdrawn or overruled.

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Previously-presented method claims 106-112 incorporate all the limitations of pending independent claim 68. Rejoinder of method claims pursuant to MPEP §821.04 was previously requested and is reiterated below. For this reason, method claims 106-112 have not been canceled in the present amendment. Applicants assume the Examiner had intended to withdraw claims 106-112 from consideration pursuant to 37 CFR §1.142(b), as being drawn to non-elected inventions. Thus, in the present amendment, these claims are indicated as "Withdrawn".

Status of and Amendments to the Claims

Further to the discussion above, claims 68, 69, 75-77, 81-83, 85-91, 93-94, 103-105 and 106-112 are believed to be pending with entry of this amendment, with claims 106-112 believed to be withdrawn from consideration. For the reasons described below, claims 70-74, 78-80, 84-85, 92, 95-102, and 113-116 are canceled herein, without prejudice to renewal or filing in a continuation or divisional application. For the reasons described below, claims 68-69, 86-87, 90, and 93 are amended herein.

Claim 68 is amended to incorporate the limitations of claim 70 (which is canceled herein), pursuant to the restriction requirement made final in the Office Action dated August 21, 2003, without prejudice to subsequent renewal or filing of the canceled subject matter in one or more continuation and/or divisional applications. Claim 68 is also amended to incorporate the limitations of claim 92 (which is canceled herein).

Claim 69 is amended to incorporate the limitations of claim 85, which is canceled herein.

Claims 71-74, 78-80 and 84 are canceled herein pursuant to the restriction requirement made final in the Office Action dated August 21, 2003, as drawn to non-elected substitutions, without prejudice to subsequent renewal or filing in one or more continuation and/or divisional applications.

Claims 86 and 87 are amended to conform claim dependencies to amended claim 69.

Claim 90 is amended to correct an inadvertent error in claim dependency. Support for this amendment is found in claim 89 from which claim 90 now depends.

Claim 93 is amended to incorporate the limitations of claim 95, which is canceled herein.

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Claims 96-102 are canceled herein as being drawn to non-elected invention Groups III and IV pursuant to the Restriction Requirement dated March 21, 2003, without prejudice to subsequent renewal or filing in one or more continuation and/or divisional applications.

None of these amendments introduce new matter into the application.

Please note that Applicants reserve the right to file subsequent applications claiming any of the canceled subject matter, and that the claim amendments and cancellations should not be construed as abandonment of any presently or previously claimed subject matter or agreement with any objection or rejection of record.

Request for Rejoinder Pursuant to MPEP §821.04

Method claims 106-112 incorporate all of the limitations of product claim 68. As discussed above, it is believed these claims are currently withdrawn from consideration pursuant to 37 CFR §1.142(b). In accordance with MPEP §821.04, Applicants request that method claims 106-112 be rejoined upon a finding of allowability of the product claims from which they depend.

Information Disclosure Statement

Applicants note with appreciation the Examiner's thorough consideration of the references cited in the Information Disclosure Statement which was submitted by Applicants on January 11, 2002 (including a four-page Form 1449 citing references designated AA-CA), as evidenced by the initialed and signed copies of the Form 1449 pages 1-4 included with the Office Action.

However, Applicants wish to note that an Supplemental IDS was submitted on July 1, 2002, with a one-page Form 1449 citing four references (numbered 1-4). A signed and initialed copy of this 1449 was not included in the recent Office Action. For the Examiner's convenience, Applicants have enclosed a copy of that one-page Form 1449 and the accompanying Information Disclosure Statement, together with a copy of the return acknowledgement postcard date-stamped by the OIPE on July 8, 2002. Applicants would appreciate receipt of an initialed and signed copy of that one-page Form 1449. Additional

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copies of the references cited therein will gladly be provided upon the Examiner's request, in the event those references are missing from the USPTO file.

Objections to the Claims (and to the Specification)

Under the heading of "Claim Objections", the Examiner noted that "The specification and claims are objected to for failing to adhere to the requirements of the sequence rules. Applicant must append SEQ ID NO's to all mentions of specific sequences in the specification and the claims. See 37 CFR 1.821(d)".

Applicants wish to direct the Examiner's attention to a communication submitted July 6, 2001, concurrent with submission of a Sequence Listing in this application, which made amendments to the specification to introduce SEQ ID NO's. It is believed the requirements of 37 CFR 1.821(d) were met at that time. **Applicants have enclosed a copy of this amendment in the event it is missing from the USPTO file.**

Applicants respectfully request clarification as to how the requirements of 37 CFR 1.821(d) are not met in the claims. The claims recite variations of SEQ ID NO:1. The first sentence of the 7th paragraph of MPEP 2422.03 states the following:

It is generally acceptable to present a single, general sequence in accordance with the sequence rules and to discuss and/or claim variants of that general sequence without presenting each variant as a separate sequence in the "Sequence Listing."

Thus, Applicants believe that both the specification and the claims are in compliance with the requirements of 37 CFR 1.821(d), and respectfully request the objections be withdrawn.

Rejection under 35 USC §112 paragraph 1

Claim 68 was rejected under 35 USC 112 paragraph 1 for allegedly failing to comply with the Written Description requirement. This rejection is respectfully traversed in part and overcome in part, for the reasons provided below.

Claim 68, as amended herein, is directed to a conjugate which comprises a polypeptide comprising an amino acid sequence which differs from SEQ ID NO:1 in 1-15 amino acid

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residues and comprises an introduced *in vivo* N-glycosylation site relative to SEQ ID NO:1, wherein the introduced *in vivo* N-glycosylation site comprises the substitution T106N; and a sugar moiety covalently attached to the introduced *in vivo* N-glycosylation site, wherein the conjugate exhibits at least 25% of the clotting activity of hFVIIa. Dependent claim 93, as amended herein, is directed to a polypeptide comprising the amino acid sequence according to claim 68, exhibiting at least 25% of the clotting activity of hFVIIa.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para 1, "Written Description" Requirement, published in the Federal Register, Vol. 66, No. 4 January 5, 2001 pp. 1099-1111 (hereinafter "Written Description Guidelines"), provides the following:

For each claim drawn to a genus: The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice [...], reduction to drawings [...], or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus [...].

In making the rejection, the Examiner stated the following:

There is a single species of the claimed genus disclosed that is within the scope of the claimed genus, i.e., SEQ ID NO:1. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described. There is substantial variability among the species" *Office Action, paragraph spanning pages 4 and 5.*

Applicants wish to clarify that the claimed genus is not SEQ ID NO:1, it is SEQ ID NO:1 comprising the substitution T106N. For the reasons presented below, Applicants maintain that the claimed genus does not have substantial variability, the exemplified species is indeed representative of the claimed genus, and, therefore, one of skill would conclude that Applicants were in possession of the claimed genus.

The specification contemplates alterations of the claimed sequence, and provides ample description of such alterations (including, for example, page 9 line 27- page 10 line 14; page 15

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line 30 – page 21 line 6; and page 28 line 5 – page 33 line 23). The specification also provides disclosure of additional conjugates contemplated by the Applicants (see, e.g., page 21 line 7 – page 33 line 23). The specification teaches procedures for making such polypeptides and conjugates which differ from SEQ ID NO:1 in 1-15 residues and which contain the substitution T106N (see, for example, page 45 line 25 – page 46 line 15, and Example 3 on pages 68-69). The specification furthermore provides an assay for detecting conjugates and polypeptides exhibiting the specified clotting activity (see, for example, page 12, lines 12-24 and page 64, lines 15-20). The specification also provides an actual reduction to practice of a conjugate having the amino acid sequence SEQ ID NO:1+T106N which exhibits the specified activity (see, e.g., Example 3 on page 69).

The claimed genus does not have substantial variation

The claimed genus does not have substantial variation, for the following reasons. All of the claimed molecules must possess the following characteristics: they must possess the specified activity, they must contain the substitution T106N, and they must differ from SEQ ID NO:1 in 1-15 amino acid residues. It is to be noted that SEQ ID NO:1 is 406 amino acids in length. Fifteen amino acid residues accounts for *less than 4%* of the residues of a 406 amino acid polypeptide. In other words, a sequence which differs from SEQ ID NO:1 in up to 15 amino acid residues is over 96% identical to SEQ ID NO:1 (since $(406-15)/406 = 0.963$).

The Examiner Training Materials, which are entitled “Synopsis of Application of Written Description Guidelines” (hereinafter “Training Materials”, which were referenced in column 1 of page 1101 of the Written Description Guidelines), in fact expressly suggests that Applicants’ claims satisfy the Written Description requirement. Example 14 on pages 53-55 of the Training Materials provides a fact scenario in which the specification claims a “protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction $A \rightarrow B$ ”, and provides an actual reduction to practice of a single disclosed species. In the analysis it is concluded that a genus of proteins having at least 95% identity to the reference sequence and exhibiting the specified catalytic activity was considered “not [to] have substantial variation”. In particular,

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There is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO: 3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by members of the genus. (*Training Materials, paragraph bridging pages 54-55*).

As noted above, the genus claimed in the present application exhibits the following relevant identifying characteristics: each member of the genus must possess the specified activity; each member of the genus must contain the substitution T106N; and each member of the genus must differ from SEQ ID NO:1 in 1-15 amino acid residues (including T106N), which, as noted above, is less variation than that of the genus described in Example 14 of the Training Materials which was determined to "not have substantial variation".

The exemplified species is representative of the genus

As noted above, there is actual reduction to practice of the species SEQ ID NO:1+T106N. The species is representative of the claimed genus because it possesses all of the relevant identifying characteristics of the genus, namely: (a) all members of the genus contain the substitution T106N, (b) all members of the genus differ from SEQ ID NO:1 in 1 to 15 residues (that is, have at least 96% sequence identity to the reference sequence SEQ ID NO:1), and (c) all members of the genus can be identified by way of the assay which Applicants have provided. Furthermore, as noted above, the claimed genus does not have substantial variation.

In light of the above, one of skill in the art would conclude from the specification that Applicants were in possession of the necessary common attributes possessed by the members of the genus claimed in claim 68 as amended herein, and claims which depend therefrom. Therefore, the specification meets the requirements of 35 USC § 112 paragraph 1 as providing

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adequate written description for the claimed invention. Applicants therefore respectfully request the rejection of claim 68 under 35 USC § 112 paragraph 1 be withdrawn.

Rejection under 35 USC §103(a)

Claims 68-70, 85-89, 91-95, and 103-105 were rejected under 35 USC § 103(a) as allegedly being unpatentable over US Patent 5,861,374 issued to Berkner *et al.* (hereinafter "Berkner"). Of the rejected claims, claims 70, 85, 92, and 95 have been canceled herein, rendering the rejection of these claims moot. The rejection of claims 68-69, 86-89, 91, 93-94, and 103-105 is respectfully traversed.

According to the MPEP at §2143, to establish a *prima facie* case of obviousness, all three of the following basic criteria must be met. First, there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference to arrive at the claimed invention. Second, there must be a reasonable expectation of success. Finally, the cited reference must teach or suggest all the claim limitations. Furthermore, the teaching or suggestion to make the claimed invention and the reasonable expectation of success must both be found in the cited art, not in Applicants' disclosure.

Claimed 68, as originally presented, was directed to a conjugate comprising a polypeptide comprising an amino acid sequence which differs from the hFVII or hFVIIa sequence SEQ ID NO:1 in 1-15 amino acid residues and comprises an introduced *in vivo* N-glycosylation site relative to SEQ ID NO:1, wherein the introduced *in vivo* N-glycosylation site comprises a substitution selected from the group consisting of T106N, I205S/T, V253N, T267N, and R315N+V317S/T; and a sugar moiety covalently attached to the introduced *in vivo* N-glycosylation site. Solely to expedite prosecution, claim 68 was amended herein in response to the requirement for restriction made final, to recite a conjugate comprising a polypeptide comprising an amino acid sequence which differs from the hFVII or hFVIIa sequence SEQ ID NO:1 in 1-15 amino acid residues and comprises an introduced *in vivo* N-glycosylation site relative to SEQ ID NO:1, wherein the introduced *in vivo* N-glycosylation site comprises the substitution T106N; and a sugar moiety covalently attached to the introduced *in vivo* N-

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glycosylation site. All of the other claims pending in this application incorporate these elements by virtue of their dependence from claim 68.

In making the rejection, the Examiner noted:

Berkner teaches pharmaceutical compositions of modified factor VII that are used to treat a variety of coagulation-related disorders, see abstract. Berkner discloses SEQ ID NO:2, which has a 99.1% query match with SEQ ID NO:1 of the instant application, GenCore version 5.1.6, page 5, result 7.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the modified factor VII of Berkner, because Berkner teaches the use of the modified factor VII in a variety of coagulation-related disorders. (*Office Action, page 6.*)

Applicants respectfully submit the Office Action does not establish a *prima facie* case of obviousness under 103(a) with respect to the cited reference. At a minimum, the Office Action does not point with any particularity to any teaching or suggestion in Berkner which would motivate one of skill to make a conjugate comprising a polypeptide comprising an amino acid sequence which differs from the hFVII or hFVIIa sequence SEQ ID NO:1 in 1-15 amino acid residues and which comprises an introduced *in vivo* N-glycosylation site relative to SEQ ID NO:1, wherein the introduced *in vivo* N-glycosylation site comprises the substitution T106N; and a sugar moiety covalently attached to the introduced *in vivo* N-glycosylation site. The Office Action does not provide any line of reasoning which would explain, when provided with the Berkner reference (and SEQ ID NO:2 therein), how one of skill would be motivated to make a conjugate comprising a sequence which differs from SEQ ID NO:1 in 1-15 amino acid residues and which contains the substitution T106N, nor, for that matter, such a conjugate which includes any of the substitutions I205S/T, V253N, T267N, or R315N+V317S/T as previously claimed.

For at least the above reasons, Applicants respectfully submit that a *prima facie* case of obviousness has not been established with respect to claim 68 as originally drafted, nor as amended herein. Furthermore, MPEP §2143.03 states that if an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious. Therefore, Applicants respectfully request the rejection of claims 68-69, 86-89, 91, 93-94, and 103-105 under 35 U.S.C. §103(a) be withdrawn.

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CONCLUSION

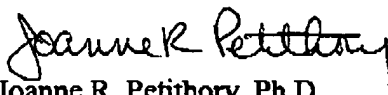
In view of the foregoing, Applicants believe the claims pending in this application are in condition for allowance. Early notification to that effect is earnestly solicited. As noted above, prior to conclusion of prosecution on the merits in this application, Applicants request rejoinder of the currently withdrawn method claims.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 298-5452.

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Respectfully submitted,


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